REMARKS

In order to further Applicants' business interests and the prosecution of the application, yet without acquiescing to the Examiner's allegations and while reserving the right to prosecute the original or similar claims in the future, Applicants herein amend Claims 79 and 80. Support for these amendments can be found throughout the Specification , for example, on page 10, lines 9-12 and Table 6, among other places. No new matter has been added.

Claims 79-84, 86-89, and 92-94 are pending following entry of Applicants amendments.

I. The Amended Claims are Enabled and Supported by an Adequate Written Description

The Examiner rejected Claims 79-81 and 83 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention (Office Action pages 2-3).

Applicants respectfully disagree.

Nonetheless, in order to further Applicants' business interests and the prosecution of the application, yet without acquiescing to the Examiner's allegations and while reserving the right to prosecute the original or similar claims in the future, Applicants have amended Claim 79.

Applicants respectfully submit that the specification describes "Dosages may range from 0.5 to 200 mg/kg/day, preferably from 3 to 25-50 mg/kg/day, given as single or divided doses, preferably given by continuous infusion or divided into two to four dosages per day." (Specification, page 10, lines 9-12). The Specification also provides support for a dose of 15 mg/kg/day.

> "As shown in table 6, a regimen of 5mg/kg lysostaphin three times daily was the most efficacious treatment. An impressive statistic is that this treatment completely sterilizied the heart valve vegetation in all but one of the rabbits. This was far superior to the standard regimen used as a positive control in this infection model: 30 mg/kg vancomycin twice daily. A regimen of 5 mg/kg lysostaphin once daily was less efficacious than the thrice daily regimen, but was almost as good as vancomycin in reducing bacterial counts in the vegetation; in fact, the effect was not statistically different from the vancomycin group." (Specification, page 20, lines 18-28, see also Table 6).

Thus, Applicants respectfully submit that Claim 79 is enabled and finds ample support in the Specification.

With regard to Claims 82 and 94, Applicants respectfully assert that"[t]he rabbit endocarditis model is now very well standardized and is accepted as a rigorous test of the ability of antimicrobial agents to cure severe human infections" (See Specification, page 23, lines 22-24; and See, e.g., Carbon, C. (1993) Experimental endocarditis: a review of its relevance to human endocarditis. *Journal of Antimicrobial Chemotherapy* **31**, *Suppl. D*, 71–85. Abstract, Appendix A; Zak, O. & O'Reilly, T. (1991). Animal models in the evaluation of antimicrobial agents. *Antimicrobial Agents and Chemotherapy* **35**, 1527–31, Appendix B; and Fantin, B. & Carbon, C. (1992). *In vivo* antibiotic synergism: contribution of animal models. *Antimicrobial Agents and Chemotherapy* **36**, 907–12, Appendix C). Accordingly, Applicants respectfully assert that the Specification reasonably conveys to one of ordinary skill in the art that the inventors at the time the application was filed had possession of the claimed invention.

Claim 85 has been cancelled rendering the Examiner's rejection moot.

Applicants respectfully request that the Examiner withdraw each rejection made under 35 U.S.C. §112, first paragraph.

II. The Amended Claims are Not Obvious

The Examiner rejected Claims 79-84, 86-89, and 92-94 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zygmunt, Goldberg and Stark, and further in view of Oldham.

Applicants respectfully disagree.

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a ***reason*** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd., 06-1329, slip op. (Fed. Cir. June 28, 2007)*, at 13-14 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be

applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR,* 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

It is well settled that the PTO "bears the initial burden of presenting a prima facie case of unpatentability.... However, when a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug,* 283 F.3d 1335, 1338 (Fed.Cir.2002). Rebuttal evidence is "merely a showing of facts supporting the opposite conclusion." In *re Piasecki,* 745 F.2d 1468, 1472 (Fed.Cir.1984). Evidence rebutting a prima face case of obviousness can include: "evidence of unexpected results," *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1369 (Fed.Cir.2007), and/or evidence "that the prior art teaches away from the claimed invention in any material respect," *In re Peterson,* 315 F.3d 1325, 1331 (Fed.Cir.2003).

Applicants respectfully assert that the cited references fail to teach or suggest the unpredictable results of the claimed invention. In addition, applicants respectfully assert that the cited references lead one of ordinary skill in the art away from the claimed invention. Applicants respectfully assert that, when properly considered, the following evidence exemplifies why the amended claims are non-obviousness.

A) The cited references lead one of ordinary skill in the art away from the claimed invention

A) Zygmunt and Goldberg

Zygmunt is a review article that discusses various properties of lysostaphin. Zygmunt reviews a number of articles, including Goldberg.

Applicants respectfully submit that the combination of Zygmunt and Goldberg do not teach or suggest all elements of the present invention, do not provide a reasonable expectation of success for carrying out the invention, and actually teach away from the claimed methods.

In particular, Applicants respectfully submit that neither reference teaches a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a

subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3 to 25 mg/kg/day (e.g., as recited in Claim 79). Moreover, the cited references do not teach or suggest administering a dose of 15 mg/kg/day (e.g., as recited in Claim 82). The cited references also fail to teach or suggest the use of recombinant lysostaphin.

Goldberg teaches that dogs administered dosages between 3-25 mg/kg/day **do not** achieve the same result as dogs administered higher doses (e.g., 50 mg/kg/day). Specifically, dogs administered lower dosages in the presently claimed range displayed an increase in lysostaphin resistant strains and also relapse.

> "The largest proportions of isolates found to be resistant were in three dogs receiving small repeated doses. The emergence of resistant isolates in these dogs may have resulted from repeated exposure to small amounts of enzyme. These three dogs relapsed, perhaps as a result of the large proportion of resistant staphylococci, or perhaps because the small doses of enzyme were insuggienct to control the infection." (Goldberg, page 52, left column, beginning at second full paragraph).

Thus, Applicants respectfully submit that Zygmunt and Goldberg not only fail to teach or suggest a method of treating an established organ infection in a human subject via administering to the subject lysostaphin in a dose of 3-25 mg/kg/day, the teachings of Zygmunt and Goldberg actually teach away from the claimed methods.

In particular, Goldberg specifically teaches that lower dosages (e.g., in the claimed range) lead to the formation of lysostaphin resistant strains. Specifically, dogs 7, and 10 exemplify why one of ordinary skill in the art would be lead away from the claimed invention. Table 4 shows that dogs 7, and 10 displayed 83 and 66 %, respectively, lysostaphin resistant strains in the blood, and dog 7 displayed 94 % lysostaphin resistant strains in tissue.

Table 1 of Goldberg indicates that dogs 7 and 10 had significant levels of staphylococci in both blood and heart valve cultures. Moreover, according to Table 1 of Goldberg, dog 7 had 3,775 colonies/ml and dog 10 had 280 colonies/ml of staphylococci in blood cultures prior to autopsy. In contrast, dogs in the "well dogs" category had no more than 5 colonies/ml in blood cultures prior to autopsy. Similarly, in heart valve cultures, dog 7 had 108 colonies/g in both aortic and mitral valve cultures whereas the dogs in the "well dogs" category had no more than 102 colonies/g in aortic valve cultures and no more than 103 colonies/g in mitral valve cultures. Moreover, according to Goldberg: [d]espite initial improvement, five dogs relapsed (relapsed

dogs) 1.5 to 2.2 days after the first dose of lysostaphin. Although additional lysostaphin was administered after the relapse occurred in dogs 8 and 10, no effect on the course ofthe infection was apparent, and dog 10 subsequently expired. (page 48 of Goldberg). The relapsed dogs are designated as Dogs 6-10 in Table I of Goldberg. Accordingly, Goldberg clearly discloses that the dogs in the "Relapsed Dogs" category, which includes Dogs 7 and 10, had a negative outcome. In fact, Dog 10 expired even though additional lysostaphin was administered after relapse occurred.

Accordingly, Applicants respectfully assert that a *prima facie* showing of obviousness has not been made with respect to the amended claims.

To the extent the Examiner has established a *prima facie* case of obviousness (Applicants do not believe a *prima facie* case has been made), Applicants respectfully put forth the following evidence. According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116F.3d 1465, 1471, 43 USPQ3d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692-93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997).

As described above, Applicants respectfully assert that the administration of dosages within the claimed range (i.e., to dogs 7 and 10) in Goldberg did not effectively treat infection of organs in the subjects and also lead to relapse in the subjects. Moreover, one of ordinary skill in the art would have had to proceed contrary to the teachings of Goldberg to arrive at the claimed invention. Thus, in order to arrive at the claimed invention, one of ordinary skill in the art would have had to employ dosages in humans which had been disclosed in Goldberg as resulting in eventual relapse and high levels of resistant strains in dogs.

Thus, Applicants respectfully submit that the cited references direct one of ordinary skill in the art away from the claimed invention. In particular, one of ordinary skill in the art would understand Goldberg, and Zygmunt summarizing the same, to teach the use of higher doses (e.g., 50 mg/kg/day or more) that provide results that were not achievable with lower dosages of the claimed invention. Goldberg did not suggest the utility of a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3-25 mg/kg/day, wherein the administering results in a 3-fold or greater reduction of staphylococci present in the subject. In fact, Goldberg teaches the avoidance of methods of treatment of the claimed invention. In particular, the ordinarily skilled person would have been motivated to select a dosage regimen for lysostaphin that is characterized by high dose (e.g., at least 50 mg/kg), and not a dose of the claimed invention (e.g., as recited in Claims 79, 94, and claims dependent thereon).

B) Stark

Applicants respectfully assert that Stark does not teach or suggest all elements of the claimed invention. That is, Stark does not teach or suggest a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3-25 mg/kg/day (e.g., as recited in Claim 79). Moreover, Stark does not teach or suggest administering a dose of 15 mg/kg/day (e.g., as recited in Claim 82). Stark also fails to teach or suggest the use of recombinant lysostaphin. Similarly, Stark does not teach or suggest a method of treating an established staphylococcal infection in a human subject, comprising: providing a subject with endocarditis; and administering to the subject a recombinantly produced lysostaphin in a dose of 15 mg/kg/day (e.g., as recited in Claim 94).

Applicants respectfully point out that it was unknown whether or not the single patient in Stark had an established infection of an organ (e.g., the heart or kidneys). Thus, Stark fails to provide a teaching, suggestion or guidance to one of ordinary skill in the art that the claimed methods would be useful. In sharp contrast, Stark actually teaches that an "episode of flushing,

mild hypotension, and tachycardia followed the intravenous administration of lysostaphin. Diphenhydramine hydocholoride (Benadryl) and epinephrine were used in the appropriate manner for anaphylaxis, and the reaction was controlled in 60 minutes." (Stark, page 240). Moreover, Stark further teaches away from the claimed invention because, to the extent that the patient's heart failure was due to bacterial infection, administration of lysostaphin did not clear such infection as the subject died as a result of congestive heart failure three days post administration of lysostaphin.

Applicants respectfully submit that the Examiner has acknowledged that Goldberg, Zygmunt and Stark, individually or in combination, fail to teach or suggest the use of recombinant lysostaphin (See, Office Action mailed 20 September 2008, page 6).

C) Oldham

Applicants respectfully submit that Oldham fails to supplement the deficiencies of Zygmunt, Goldberg and/or Stark to suggest the claimed invention. In sharp contrast, Oldham actually leads one of ordinary skill in the art away from the claimed invention.

Oldham teaches the treatment of bovine mastitis using recombinant lysostaphin. Oldham does not suggest a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3-25 mg/kg/day (e.g., as recited in Claim 79). Moreover, Oldham does not teach or suggest administering a dose of 15 mg/kg/day (e.g., as recited in Claims 82 and 94). Similarly, Oldham does not teach or suggest a method of treating an established staphylococcal infection in a human subject, comprising: providing a subject with endocarditis; and administering to the subject a recombinantly produced lysostaphin in a dose of 15 mg/kg/day (e.g., as recited in Claim 94).

Applicants respectfully submit that the cited references, individually or in combination, do not render predictable the claimed methods of the present invention. In particular, work with lysostaphin in the cited references showed limited reduction in kidney bacterial load in mouse models (e.g., in Zygmunt) and in heart valves and other organs in a dog endocarditis model (e.g., Goldberg) at doses ranging from 50 to 250 mg/kg treatment. Despite these high dosages used, effectiveness of the magnitude required in the treatment of severe staphylococcal infections was

not observed. That is, the cited references would not have led one of ordinary skill in the art to predict the rapid and total sterilization (e.g., of heart valve vegetations) in subjects treated with a lysostaphin regimen of the claimed methods. Moreover, one of ordinary skill in the art could not have predicted, prior to the disclosure of the present invention, the unexpected effectiveness of a lysostaphin regimen of the claims against *S. aureus* compared to conventional treatments available in the art at the time of the invention.

Accordingly, Applicants respectfully request that the rejection of the Claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Respectfully submitted,

Date: 16 June 2009

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